CLINICAL PHARMACOLOGY REVIEW

Date: October 5, 1999; October 29, 1999; November 1, 1999 (final)

From: Lori A. Paserchia, MD (LP)

Through: Martin D. Green, PhD MD
Karen Weiss, MD/Director, Div of Clinical Trial Design and Analysis

Subject: Clinical Pharmacology Review of BLA 99-0128, Remicade (Supplement) (Crohn's)

To: Center/Division/Office- DARP, OTRR
Primary Reviewer- Barbara Matthews, MD

Please see attached review.

EXECUTIVE SUMMARY

Infliximab (Remicade, cA2) is a chimeric IgG1κ monoclonal antibody produced by a recombinant cell line from a genetically-engineered form of the mouse monoclonal antibody prototype, A2. Infliximab binds with high affinity to soluble and transmembrane human TNFα. The resultant inhibition of TNFα binding with its receptors prevents the biological activities of TNF α including: induction of pro-inflammatory cytokines such as IL-1 and IL-6, and enhancement of leukocyte migration and activation. Infliximab is normally-glycosylated and has an approximate molecular weight of 149,100 daltons.

Infliximab is currently licensed for the reduction of signs and symptoms in rheumatoid arthritis (RA) patients who have an inadequate response to methotrexate. It is also licensed for the reduction of signs and symptoms in Crohn's disease. This supplement to the BLA (sBLA) contains safety, efficacy and pharmacokinetic (PK) data in support of a revised indication for RA: for the treatment of patients with RA in combination with methotrexate (MTX) for the reduction of signs and symptoms in patients who have had an inadequate response to MTX.

The sBLA contains PK results from 6 studies. Serum infliximab levels were collected in ail 6 studies but the derivation of PK parameters (e.g., clearance, volume of distribution) was performed in only 3 of these 6 studies (protocols C0168T09, C0168T15/17, C0168T18). Four of the 6 submitted studies investigated a prototype, — formulation whereas only 1/6 investigated the to-be-marketed, lyophilized formulation (protocol T0168T22). One study investigated both formulations (protocol C0168T18). Varying intravenous doses were studied including 1, 3, 5, 10 and 20 mg/kg. In addition to single dose, different dose schedules were also studied including every-2-weeks for 3 doses (protocol C0168T07), at weeks 0, 2, 4, 10 and 14 (protocol C0168T14), every-8-weeks for 3 doses (CO1 68T15/17), and at weeks 0, 2 and 6 followed by either every-4-weeks or every-8-weeks (protocol CO1 68T22). Finally, only 3 studies (protocols C0168T14 [1/2 the subjects], C0168T15/17, C0168T22) required the concurrent administration of MTX, as proposed for this new indication.

The data generally support a dose-proportional PK profile for the 3 and 10 mg/kg dose levels of infliximab plus MTX. A dose-efficacy response or concentration-efficacy relationship is not evident for either the 3 or the 10 mg/kg dose level when given every-4-weeks or every-8-weeks with MTX. However, in the absence of concurrent MTX administration, a dose/concentration- efficacy relationship was evident in 1/6 studies (protocol C0168T14). A dramatic decrease in serum infliximab concentration for the 1 mg/kg dose given without concurrent MTX was associated with a definite decline in efficacy. The PK results for the proposed 3 mg/kg dose, and for the IO mg/kg dose, did not demonstrate the same degree of decline in concentration in the absence of concurrent MTX use.

HACA formation is a possible reason for the increase in infliximab Cl and resultant decrease in serum concentration. Fifty-seven percent of subjects who received 1 mg/kg without MTX became HACA positive versus only 25% and 10% in the 3 and IO mg/kg groups, respectively.

The PK data from 1 of the 6 studies (protocol C0168T09) revealed a statistically significant gender-related difference in clearance (Cl) with males having a consistently higher median Cl than females. This difference was most predominant for the lowest dose studied, 1 mg/kg. The difference for the proposed 3 mg/kg dose was very slight. An associated change in median volume of distribution was not seen. This difference in Cl was not found in the other 2 studies where derivation of PK parameters was performed however the sample size in each was small.

The reason for this difference in Cl has yet to be determined although HACA formation once again may be involved, especially given the lack of concurrent MTX administration. Sixty percent of males, compared to 35% of females, were HACA positive in the 1 mg/kg dose group. The difference in median Cl was associated with a difference in exposure based on the median area-under-the-curve (AUC) but the clinical impact of these differences is not readily apparent in this study based on the data submitted. The gender-related difference in median Cl, and resultant median AUC, was not as pronounced for the proposed dose of 3 mg/kg.

At this time, insufficient data are available to comment upon the trend noted in the safety database of a greater frequency of liver function enzyme elevation and stomatitis (known MTX-related adverse events) in subjects

receiving infliximab and MTX compared to those subjects receiving infliximab alone. If warranted based on post-marketing surveillance, a format drug-drug interaction study could be conducted.

The potential for adverse events such as serum sickness upon re-initiation of infliximab therapy is unknown due to the lack of a database comprised of the pertinent population that is of sufficient size.

The PK results submitted in this sBLA do not present a barrier to licensure of the proposed dosing regimen of 3 mg/kg infliximab. The Pediatric Rule applies to this sBLA and been addressed with the sponsor by Dr. Barbara Matthews.

Clinical Pharmacology Review of BLA 99-0128 (infliximab, Remicade)

PK Studies Summary:

1. Protocol CO168T07. **Review on Page 3**

Phase 1 Study of Chimeric Anti-TNF in Patients with Rheumatoid Arthritis; an open-label, safety, tolerance, immunogenicity, pharmacokinetics and clinical response trial with infliximab in patients with advanced rheumatoid arthritis. Subjects were given either an infusion of 10 mg/kg infliximab that was repeated 2 weeks later (n= 15) or 4 infusions of 5 mg/kg every 4 days (n= 5). There was also an extended treatment phase where eligible subjects received 3 additional infusions of 10 mg/kg at 2 week intervals. This protocol used only the — Formulation of infliximab and did not investigate the to-be-marketed lyophilized formulation. Treatment with methotrexate was excluded.

2. Protocol CO168T09 **Review on Page 5**

Placebo Controlled Phase 2 Study of Chimeric Anti-TNF in Patients with Rheumatoid Arthritis; 3-arm, multicenter, randomized, double-blinded, single-dose, pharmacokinetic trial in subjects with advanced rheumatoid arthritis and an escape clause at 6 months for lack of response or relapse of disease. Doses studied were 1 or 10 mg/kg iv during the blinded phase and 1, 3, 10, or 20 mg/kg iv during the open-label phase. This protocol investigated only the — formulation. Concurrent use of methotrexate was not permitted.

3. Protocol CO168T14 **Review on Page 14**

Phase 2 Multicenter Study of Chimeric Anti-TNF Monoclonal Antibody (infliximab) in Adjunct to Methotrexate Treatment in Patients with Rheumatoid Arthritis. A randomized 7-parallel arm, multicenter, double-blind, placebo-controlled study that examined the safety, efficacy and PK of 1, 3, and 10 mg/kg infliximab iv with or without concurrent use of methotrexate 7.5 mg/week. Infliximab doses were given on Day 0, and Weeks 2, 4, 10 and 14. There were 15 subjects per arm. The — formulation was used.

4. Protocol CO168T15/T17 **Review on Page 19**

Single-Dose (T15)/ Repeat-dose treatment extension (T17) Study of Chimeric Anti-TNF Monoclonal Antibody (infliximab) in Patients with Active Rheumatoid Arthritis Who Are Receiving Methotrexate Therapy. This was a Phase 2 trial using the — formulation of infliximab in subjects receiving a stable course of methotrexate. In T15, a single dose of placebo, 5, 10 or 20 mg/kg iv was given; there were 7 subjects per dose level. In T17, 23 subjects received 10 mg/kg iv x 3 every 8 weeks.

5. Protocol C0168T18 **Review on Page 23**

Tumor Necrosis Factor (TNF) Blockade in Patients with Rheumatoid Arthritis: Mechanisms of Action; an open-label, single-dose study in IO subjects with active rheumatoid arthritis given IO mg/kg iv. One goal of the protocol was to compare the PK profile of the to-be-marketed lyophilized formulation (n= 5) to the — Formulation used in prior protocols (n= 5).

6. Protocol CO168T22 **Review on Page 25**

A placebo-controlled, double-blinded, randomized clinical trial of anti-TNF chimeric monoclonal antibody (cA2; infliximab) in patients with active rheumatoid arthritis despite methotrexate treatment (ATTRACT). This is a 5-arm, multicenter, Phase 3 study in subjects with rheumatoid arthritis who are on a stable dose of at least 12.5 mg/week of methotrexate. The dose levels are placebo, 3 or 10 mg/kg iv. All dose levels are given at week 0, 2 and 6 followed either by every 4 week dosing thereafter (placebo, 3 and IO mg/kg) or every 8 weeks thereafter (3 or IO mg/kg). The lyophilized Formulation is being administered (lots ———————— , and — Study dates: 3/97 - ongoing; the results from 3/97 to 8/98 (n= 200) have been submitted in this BLA.

Individual Study Review:

In General

- Proposed dosing regimen: 3 mg/kg iv once during weeks 0, 2, and 6 and then q 8 weeks, in combination with methotrexate (MTX).

- infliximab assay: a polyclonal rabbit antibody-based sandwich enzyme immunoassay (EIA) was used to determine serum infliximab concentrations (limit of detection [LOD]= 0.390 ug/mL) for protocols T07and T09. In protocols T14, T15/17, T18 and T22, serum concentrations of infliximab were determined with a monoclonal-based enzyme immunoassay (EIA) method (LOD= 0.10 µg/mL).

- HACA assay: human antichimeric antibody (HACA) levels were determined with a "double antigen" analysis format. This assay is unable to determine the HACA concentration if free infliximab is present in the serum. To date, the sponsor has been unsuccessful in overcoming this problem.

- PK parameter derivation: when planned for in a protocol, pharmacokinetic (PK) parameters were derived using noncompartmental methods: AUCO-inf and AUMC were calculated using a combination of linear and log-linear trapezoidal rules with extrapolation to infinity; dose-normalized AUC (AUC/dose), Cmax (by observation), Cl (Cl=dose/AUC), Vdss (Vd =MRTxCl), MRT was calculated from AUMC/AUC without correction for the 2 hour infusion time which is negligible relative to the terminal half-life; terminal rate constant and t1/2 were obtained by log-linear regression. The Wilcoxon Rank Sum Test was used to determine statistical significance.

1. Protocol C0168T07: Phase 1 Study of Chimeric Anti-TNF in Patients with RA.

Methods

This protocol was for an open-label, safety, tolerance, immunogenicity, PK and clinical response trial in patients with advanced RA. Subjects were given either an infusion of 10 mg/kg infliximab that was repeated 2 weeks later (n= 15) or 4 infusions of 5 mg/kg infliximab every 4 days (n= 5). A test dose was used: 0.1 mL diluted to 10 mL with normal saline and given iv over 5 minutes. There was also an extended treatment phase where eligible subjects received 3 additional infusions of 10 mg/kg at 2 week intervals. This protocol used only the — formulation of infliximab (lot —— and did not investigate the to-be-marketed (TBM) lyophilized formulation. Subjects were required to have halted disease modifying antirheumatic drugs (DMARD) therapy at least 4 weeks prior to treatment. Concomitant DMARD therapy was excluded. Concurrent and stable use of oral steroids or NSAIDs was permitted. Study dates: 5/92 - 7/94.

Serum infliximab concentration was measured at predose and at 1, 2, 4, 8, 12, and 24 hours after completion of the first and last infusions; if possible, a 48-hour sample was also obtained. For those subjects receiving treatment every 4 days, samples were also obtained before and at 1 and 24 hours after the second and third infusions. No plans were included in the protocol for the derivation or analysis of PK parameters. HACA levels were determined periodically for 8 weeks after the start of treatment.

Results

All subjects completed all infusions except Subject 01015 who developed bronchitis and did not receive the second dose of 10 mg/kg. Total infusion volume was 300 mL and duration was 2 hours. Ten subjects who demonstrated a clinical response to infliximab participated in the extended treatment phase.

PK

Individual subject data and summary statistics for the serum infliximab concentrations were submitted but PK parameters were not reported. The log concentration v. time curves are located on the next page. Accumulation was seen in the subjects receiving 5 mg/kg every 4th day whereas accumulation was not found in the subjects receiving 2 doses of 10 mg/kg dose separated by 14 days. Otherwise, the PK information from this protocol is not very helpful.

HACA

Evaluable HACA levels were found in 13/20 subjects; the remaining samples were not evaluable due to the presence of infliximab in the serum samples. 0/4 evaluable subjects in the 5 mg/kg arm, 1/7 subjects in the 10 mg/kg arm, and 4/6 subjects in the extended phase developed a positive HACA response. This produced a total HACA response of 5/13 (39%) where 2/5 had titers of 1:20, 2/5 had 1:80, and 1/5 had 1:20480. The subject with the 1:20480 titer first developed HACA after the first dose in the extended phase after receiving 5 mg/kg during the initial phase of the study. This subject was asymptomatic until after the third dose in the extended phase when mild flushing, fever and headache occurred.

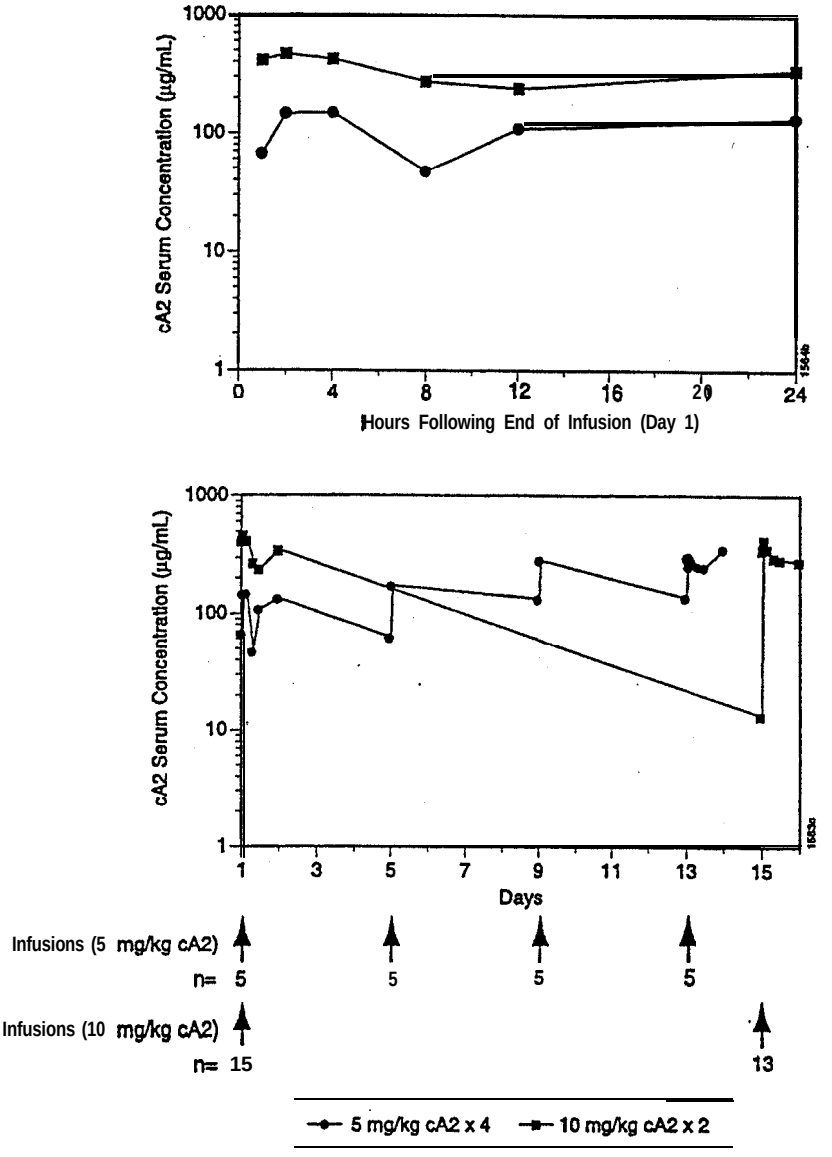


Figure 1 **Median serum cA2 concentration over the first 24 hours following the end of the first cA2 infusion (top panel) and median cA2 serum concentration over time for the 2 treatment groups during the core study (bottom panel).**

2. Protocol C0168T09: Placebo Controlled Phase 2 Study of Chimeric Anti-TNF in Patients with RA.

Methods

This protocol was for a 3-arm, multicenter, randomized, double-blinded, single-dose, PK trial in subjects with advanced RA with an escape clause at 4 weeks for lack of response, or at up to 6 months for relapse of disease. This was a 2-phase study: a blinded phase, and an open-label phase. A single dose of placebo, 1 or 10 mg/kg iv was given during the blinded phase (n= 24/dose level except for n= 25 for the 1 mg/kg group). A single dose of 3, IO, or 20 mg/kg iv was given during the open-label phase (n= 33, 16 and 17, respectively). Only the -- formulation (lot ——— was given. DMARD therapy was halted at least 4 weeks prior to, and during, the study. Concurrent and stable use of oral steroids or NSAIDs was permitted. Study Dates: 9/93 to 9/94.

Serum infliximab levels were measured at predose and at 5 minutes, 1, 2, 4, 8, 12, 24 and 72 hours, 1, 2, 4 weeks, and 2 and 4 months postinfusion (during both the blinded and open-label phases). Derivation of PK parameters was planned. HACA monitoring was performed during the blinded and/or open-label infusion at predose, 2 and 4 weeks, and 2, 4 and 6 months after the infusion(s) if the subject was still responding.

Results

PK

The final PK assessment was based on n= 25 for the 1 mg/kg dose, n= 14 for the 3 mg/kg, n= 29 for the 10 mg/kg, and n= 3 for the 20 mg/kg dose. The PK data from the 20 mg/kg group will not be evaluated due to the small sample size. The variable total sample sizes were due to the inclusion of PK data from subjects given placebo originally who then entered the open-label phase. Three subjects (1 initially given 1 mg/kg, and 2 initially given 10 mg/kg) did not return to a baseline serum infliximab level prior to entering into the open-label phase but the levels are not significantly high enough to confound the PK assessment. Exposure increased in a dose-proportional manner from 1 to 3 mg/kg and in a slightly greater than dose-proportional manner from 3 to 10 mg/kg. There was an associated decrease in the median CL, especially from 3 to 10 mg/kg, without a clinically significant change in the Vss. Accordingly, the elimination t1/2 increased with increasing dose level with a median value of 192 hrs (8 days) for the 3 mg/kg dose (single dose and without concomitant MTX). A table of these results, and a log concentration v. time curve can be found on pages 7-9.

The sponsor's demographic subset analysis revealed a statistically significant difference in median Cl between males (n= 16) and females (n= 55) across all dose levels (20.8 v. 13.4 mL/hr, respectively; p= 0.008). This difference was not associated with a significant difference in Vd between males and females. There was no relationship to age or weight. As shown in the table on page IO, when the database is subdivided by dose, the difference in median Cl between males and females is found to be greatest for the 1 mg/kg dose:

Dose	Median difference in Cl between genders
1 mg/kg	12 mL/hr
3 mg/kg	4.9 mL/hr
10 mg/kg	6.4 mL/hr

The greater difference in median Cl for the 1 mg/kg dose may be related to greater HACA formation. A table of the summary PK results by gender and HACA status for the 1 mg/kg dose located on page 11 demonstrates that 60% (3/5) of the males had a positive titer (1:40 or less) versus 35% (7/20) of the females. Limitations of these data include the small sample size-- especially for the males, the single-dose nature of the database, and the lack of concurrent MTX use (which can affect HACA formation).

The summary PK results by gender and HACA status for the 3 mg/kg and for the 10 mg/kg doses can be found on pages 12 and 13, respectively. As for the 1 mg/kg dose, slightly higher median Cl is found in the HACA+ subjects regardless of gender for the 3 mg/kg dose. A slightly higher median Cl is also found in males

compared to females, regardless of HACA status. For the 10 mg/kg dose, HACA status did not impact on the median Cl in females, however once again, males had a slightly higher median Cl compared to females. The impact on median AUC of these differences in Cl due to gender was examined (see the table on page 10). For the proposed dose of 3 mg/kg, a difference of 1292 ug/mL*hr was found in the median AUC between males and females with the males having the higher median AUC. Based on HACA status (table on page 12), HACA+ subjects clearly had a lower median AUC compared to the HACA- subjects:

	Median AUC	
	females	males
HACA+	**8405** (n= 4)	**7450** (n= 1)
HACA-	12720 (n= 6)	11639 (n= 3)

HACA

During the blinded phase, 45/49 subjects had evaluable HACA results of which 16/45 (35.6%) were positive. The 1 mg/kg dose group had a higher proportion of positive HACA (10/24= 42%) than did the 10 mg/kg dose group (6/21= 29%). All of the titers were 1:40 or less.

13/16 subjects who were HACA positive after the blinded infusion proceeded to receive a second infusion during the open label phase. 8 of these 13 (62%) subjects remained positive after the open-label infusion; for 6/8, the titer was 1:80 or greater. Interestingly, the 2/8 subjects with the highest titer (1:1280, 15120) did not experience any AE's whereas 5/8 of subjects with titers of 1:20 to 1:80 had either mild urticana (n= 1), mild pruritus (n= 1) or prolonged hospitalization (n= 3) due to infusion-related moderate fever and erythematosus rash, mild drowsiness, severe arthralgia/myalgia, or mild to moderate nausea/vomiting.

49 subjects who were HACA negative after the blinded dose proceeded to the open-label phase and had evaluable HACA assay results. 21 of these 49 (43%) became HACA positive after the open-label infusion. The titers for these subjects tended to not be as elevated; only 2 subjects had a titer greater than 1:40 (1:80, 1:640). There were no reports of AE's.

Table 1 Pharmacokinetic parameters of infliximab following initial treatment[a] of patients with rheumatoid arthritis

	Dose of Infliximab				
	1 mg/kg	3 mg/kg	10 mg/kg	20 mg/kg	p-Value
C_{max} (µg/mL)					
Pts evaluated	25	14	29	3	
Mean ± SD	27.6 ± 10.8	78.3 ± 26.4	292.9 ± 86.2	632.3 ± 199.6	
Median	23.1	77.3	277.0	603.0	< 0.001
Interquartile range					
Range					
AUC (µg/mL x hr)					
Pts evaluated	25	14	29	3	
Mean ± SD	4562 ± 3524	11765 ± 4800	52463 ± 14157	84920 ± 16113	
Median	3672	11065	54775	82409	< 0.001
Interquartile range					
Range					
AUC/dose (kg x hr/mL)					
Pts evaluated	25	14	29	3	
Mean ± SD	4.5 ± 3.5	3.9 ± 1.6	5.2 ± 1.4	4.2 ± 0.8	
Median	3.7	3.7	5.5	4.1	0.027
Interquartile range					
Range					
Clearance (mL/hr)					
Pts evaluated	25	14	29	3	
Mean ± SD	20.0 ± 8.9	18.1 ± 5.8	14.1 ± 5.1	15.2 ± 1.9	
Median	18.6	17.9	12.1	15.3	0.030
Interquartile range					
Range					

continued

Table 1 Pharmacokinetic parameters of infliximab following initial treatment[a] of patients with rheumatoid arthritis (continued)

	Dose of Infliximab				
	1 mg/kg	3 mg/kg	10 mg/kg	20 mg/kg	p-Value
Volume distribution at steady state (mL)					
Pts evaluated	25	14	29	3	
Mean ± SD	3917 ± 1468	4679 ± 1781	3989 ± 911	3527 ± 950	
Median	3893	4117	4094	3430	0.426
Interquartile range					
Range					
Mean residence time (hrs)					
Pts evaluated	25	14	29	3	
Mean ± SD	221 ± 96	273 ± 103	301 ± 90	232 ± 55	
Median	180	267	299	201	0.008
Interquartile range					
Range					
Terminal half-life (hrs)					
Pts evaluated	25	14	29	3	
Mean ± SD	144 ± 76	218 ± 126	218 ± 73	174 ± 90	
Median	110	192	219	125	0.018
Interquartile range					
Range					

[a] Initial treatment at dose indicates, in either blinded or open-label phase.

concluded

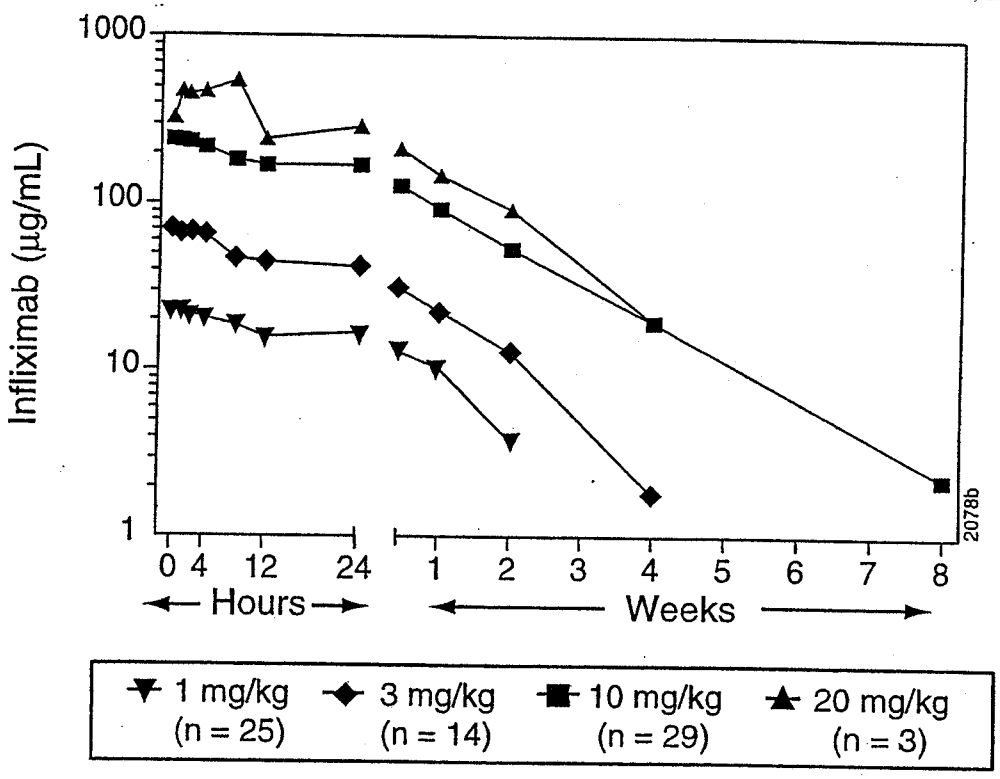


Figure 17 **Median serum infliximab concentration over time profile following an initial infusion of 1, 3, 10 or 20 mg/kg administered during either the blinded or open label phase of the study.** The median concentrations over time following an initial treatment with 1, 3, 10 or 20 mg/kg of infliximab are shown using diamond, circle, square and triangle symbols, respectively. The number of patients in each treatment group are shown in the figure legend. The first set of results shown after the break in the x-axis was obtained at 72 hours following the end of the infusion.

T09: Summary statistics for PK parameters by dose level and gender; single dose, -MTX

	gender	age	wt (kg)	AUC0,inf (ug/mL*hr)	Cl (mL/hr)	vd (mL)	mrt (hrs)	t1/2beta (hrs)
1 mg/kg								
mean	females n=20	56	67	4245	18.4	3707	220	148
median		62	68	3913	18.2	3721	189	113
SD		13	10	1998	7.2	1338	93	83
MIN								
MAX								
mean	males n= 5	59	81	5830	26.3	4758	225	124
median		60	83	2540	30.3	4766	175	107
SD		9	11	7282	13.0	1821	119	33
MIN								
MAX								
3 mg/kg								
mean	females n=10	50	61	11534	17.6	4723	282	221
median		50	60	11065	15.9	4140	267	192
SD		14	8	4121	6.2	1736	98	120
MIN								
MAX								
mean	males n= 4	49	71	12343	19.5	4567	253	210
median		53	71	9773	20.8	3865	260	202
SD		13	16	6947	5.2	2164	129	159
MIN								
MAX								
10 mg/kg								
mean	females n=24	49	67	54883	12.9	3938	319	231
median		54	64	55262	11.9	4099	321	253
SD		12	12	12951	3.6	903	86	70
MIN								
MAX								
mean	males n= 5	52	75	40849	20.3	4232	219	157
median		56	83	45881	18.3	4094	194	133
SD		14	13	15323	6.8	1014	61	60
MIN								
MAX								

T09: SUMMARY PK BY GENDER AND HACA STATUS FOR SINGLE DOSE 1 MG/KG -MTX

subject	gender	age	wt (kg)	AUC0,inf (ug/mL*hr)	Cl (mL/hr)	Vd (mL)	MRT (hrs)	t1/2beta (hrs)
HACA POSITIVE								
mean	females	57	67	3340	22	3803	184	135
median	n= 7	62	68	3125	23	3893	154	110
SD		16	6	1221	8	933	71	74
MIN								
MAX								
mean	males	56	85	2735	32	5396	170	105
median	n= 3	60	82.6	2540	30.3	4766	174	104
SD		7	11	366	6	1287	12	2
MIN								
MAX								
HACA NEGATIVE								
mean	females	55	67	4732	16	3655	239	155
median	n= 13	61	68	4148	14	3510	197	122
SD		12	12	2201	6	1546	99	90
MIN								
MAX								
mean	males	62	76	10474	18	3800	307	154
median		62	75.75	10473.5	18.35	3799.5	306.5	153.5
SD	n= 2	13	11	11832	20	2625	186	39
MIN								
MAX								

T09: SUMMARY PK BY GENDER AND HACA STATUS FOR SINGLE DOSE 3 MG/KG -MTX

subject	gender	age	wt (kg)	AUC0,inf (ug/mL*hr)	Cl (mL/hr)	Vd (mL)	MRT (hrs)	t1/2beta (hrs)
HACA POSITIVE								
mean	females	41	59	9562	20	5212	271	187
median	n= 4	39	59	8405	20	4346	242	144
SD		8	4	3885	8	2228	109	140
MIN								
MAX								
mean	males	30	60	7450	24.2	2840	118	64
median	n= 1							
SD								
MIN								
MAX								
HACA NEGATIVE								
mean	females	57	63	12849	16	4398	289	244
median	n= 6	57	61	12720	14	4140	267	251
SD		13	11	4040	5	1460	100	112
MIN								
MAX								
mean	males	56	74	13974	18	5143	298	259
median	n= 3	54	81.1	11639	20.7	4224	352	321
SD		5	17	7512	5	2243	113	154
MIN								
MAX								

T09: SUMMARY PK BY GENDER AND HACA STATUS FOR SINGLE DOSE 10 MG/KG -MTX

subject	gender	age	wt (kg)	AUC0,inf (ug/mL*hr)	Cl (mL/hr)	Vd (mL)	MRT (hrs)	t1/2beta (hrs)
HACA POSITIVE								
mean	females	49	65	52258	13	3780	304	220
median	n= 7	54	64	54775	12	3650	311	202
SD		13	8	9639	3	799	82	74
MIN								
MAX								
	males							
	n= 0							
HACA NEGATIVE								
mean	females	51	69	54371	13	3716	290	206
median	n= 13	54	65	56189	12	3851	305	195
SD		14	9	9765	5	892	82	83
MIN								
MAX								
mean	males	52	75	40849	20	4232	219	157
median		56	83	45881	18.3	4094	194	133
SD	n= 5	14	13	15323	7	1014	61	60
MIN								
MAX								

3. Protocol C0168T14: Phase 2 Multicenter Study of Chimeric Anti-TNF Monoclonal Antibody (infliximab) in Adjunct to Methotrexate Treatment in Patients with Rheumatoid Arthritis.

Methods

A randomized 7-parallel arm, multicenter, double blind, placebo-controlled study that examined the safety, efficacy and PK of 1, 3, and 10 mg/kg infliximab iv with or without concurrent use of stable methotrexate (MTX) dose of 7.5 mg/week. Infliximab doses were given on Day 0, and Weeks 2, 4, 10 and 14. There were 15 subjects per arm. The [redacted] formulation was used (lot [redacted]). DMARD therapy other than MTX was not permitted. Concurrent and stable use of oral steroids or NSAIDs was permitted. Study dates: 9/94 - 7/95.

Peak and trough serum infliximab concentrations were measured at predose, 1 hour after each infusion (weeks 0, 2, 6, 10 and 14) and at weeks 1, 4, 8, 12, 16, 18, 20, 22 and 26. PK parameters were not derived. Evaluation of HACA formation was obtained before the first infusion and at weeks 2, 6, 10, 14, 18 and 26.

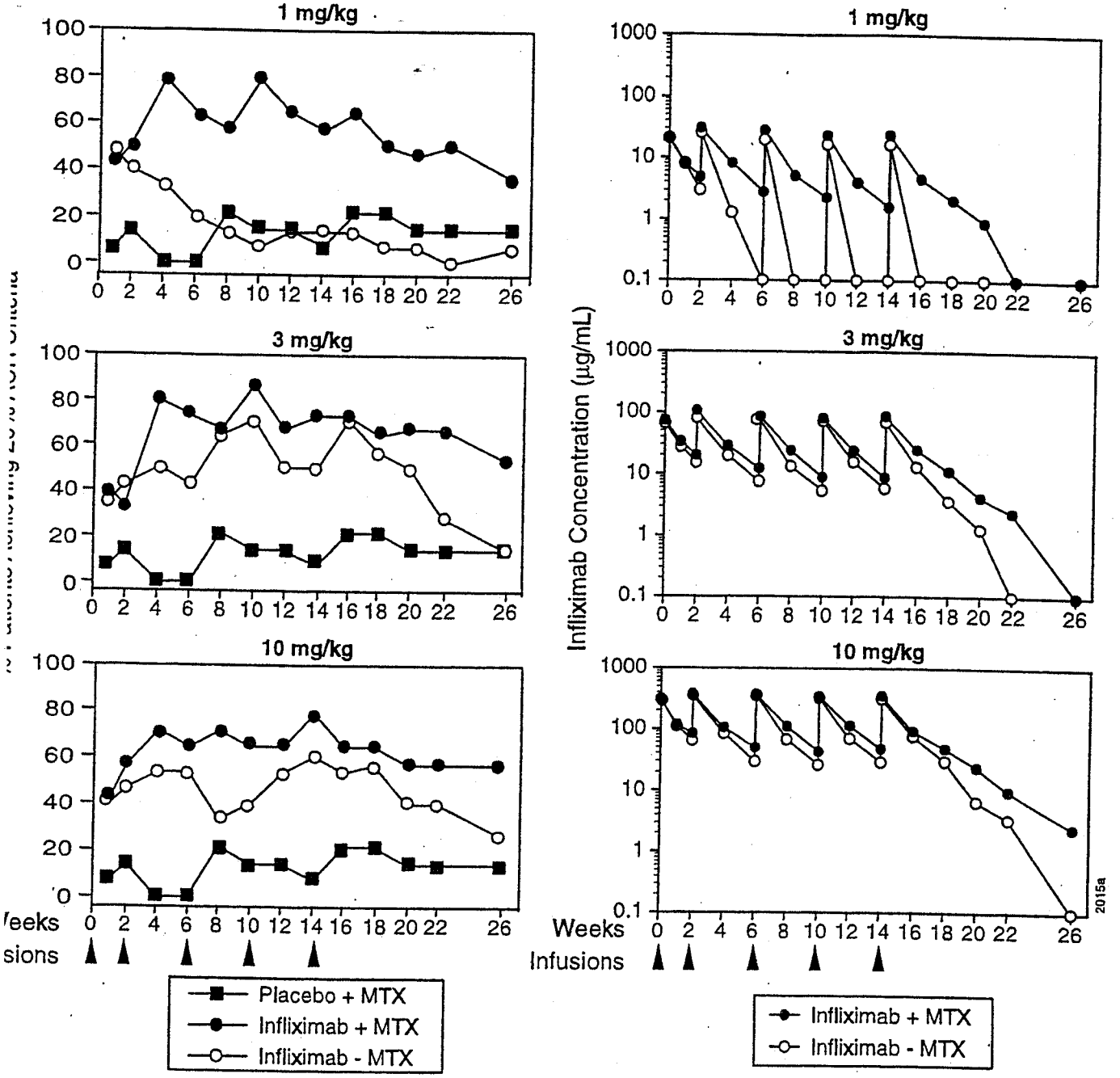
Results

PK

The serum infliximab log concentration v. time curves and summary statistics can be found on pages 15-17. The log concentration v. time curves on the right-hand side of page 15 show that the Cmax is roughly dose-proportional regardless of the presence or absence of MTX. Significant accumulation is not evident past week 2. Observation of the curves for the 3 and 10 mg/kg doses reveals a slight increase in the AUC when MTX is given concurrently compared to the AUC without MTX. This difference is drastic for the 1 mg/kg dose, however. An increase in infliximab Cl due to the formation of HACA in the subjects not receiving concurrent MTX is a possible explanation: MTX inhibits HACA formation regardless of infliximab dose level. In the absence of MTX, the immunosuppressive ability of the 3 and 10 mg/kg doses are sufficient to inhibit HACA formation whereas this ability is not sufficient for the 1 mg/kg dose. The increased Cl and resultant decreased AUC of the 1 mg/kg dose without MTX is associated with a sharp decrease in clinical response (as shown in the left-hand graphs on page 15). The difference in efficacy AUC between infliximab without MTX and infliximab with MTX is not as drastic for the proposed dose of 3 mg/kg or for the 10 mg/kg dose.

HACA

The table on page 18 shows a summary of the HACA response. Twenty-five percent (15/60) of all subjects in the study had a positive HACA response. The greatest number of subjects had a titer of 1:160 (5/15= 33%), followed next by a titer of 1:80 (4/15= 27%). Only 1 subject had a higher titer (1:2560). The frequency of HACA+ subjects decreased with increasing dose: 37% (10/27) for 1 mg/kg, 19% (4/21) for 3 mg/kg, and 8% (1/12) for 10 mg/kg. This trend persists when MTX use is also considered, with the frequency of HACA+ subjects consistently higher in subjects who did not receive MTX concurrently. The dose group with the highest frequency of HACA+ was the 1 mg/kg without MTX group (8/14= 57%). For the proposed dose of 3 mg/kg with MTX, the frequency was 1/9= 11%.



Comparison of the percentage of patients achieving ≥ 20% ACR response and median serum infliximab concentrations in C0168T14. The percentage of patients achieving or exceeding the 20% ACR criteria are shown in the left panels, and the median serum infliximab serum concentrations for the same treatment groups are shown in the panels on the right side. The infliximab doses administered are indicated by arrows on the bottom left and right side figures. In this figure, median concentrations of infliximab which are below the limit of detection for the assay (<0.1 µg/mL) are shown as equal to 0.1 µg/mL.

Table 1.1 Serum infliximab concentration (µg/mL)

	Treatment Group						
	Placebo	1 mg/kg infliximab		3 mg/kg infliximab		10 mg/kg infliximab	
	MTX+ (n=14)	MTX+ (n=14)	MTX- (n=15)	MTX+ (n=15)	MTX- (n=14)	MTX+ (n=14)	MTX- (n=15)
Baseline							
Pts evaluated	14	14	15	15	14	14	15
Mean ± SD	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Interquartile range	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)
Range	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)	(0.0, 0.0)
Post-infusion 1[a]							
Pts evaluated	14	14	15	15	14	14	15
Mean ± SD	0.0 ± 0.0	23.5 ± 7.4	21.8 ± 8. 0	75.4 ± 15.6	64.7 ± 10.5	324.0 ± 76.2	284.0 ± 56.5
Median	0.0	21.3	20.4	73.5	66.5	306.5	309.0
Interquartile range							
Range							
1 week							
Pts evaluated	14	14	14	15	14	14	14
Mean ± SD	0.0 ± 0.0	9.9 ± 5.6	7.7 ± 1.9	32.3 ± 7.6	28.6 ± 6.8	117.7 ± 27.0	109.7 ± 3.16
Median	0.0	8.1	8.0	33.0	27.6	116.0	111.0
Interquartile range							
Range							
2 weeks							
Pts evaluated	14	14	15	15	14	14	15
Mean ± SD	0.0 ± 0.0	5.3 ± 2.3	3.4 ± 1.8	19.3 ± 5.7	16.0 ± 5.8	77.0 ± 19.0	64.4 ± 21.6
Median	0.0	4.8	3.0	20.0	15.4	83.9	65.4
Interquartile range							
Range							
Post-infusion 2[a]							
Pts evaluated	13	14	15	15	14	14	15
Mean ± SD	0.0 ± 0.0	29.8 ± 7.7	25.9 ± 8.3	105.3 ± 22.7	81.9 ± 14.9	407.9 ± 84.3	356.6 ± 94.6
Median	0.0	30.2	25.8	106.0	81.5	375.5	353.0
Interquartile range							
Range							

continued

Table 1.1 Serum infliximab concentration (µg/mL) (continued)

	Treatment Group						
	Placebo	1 mg/kg infliximab		3 mg/kg infliximab		10 mg/kg infliximab	
	MTX+ (n=14)	MTX+ (n=14)	MTX- (n=15)	MTX+ (n=15)	MTX- (n=14)	MTX+ (n=14)	MTX- (n=15)
4 weeks							
Pts evaluated	11	14	15	15	14	14	15
Mean ± SD	0.0 ± 0.0	8.0 ± 4.6	2.5 ± 3.0	32.0 ± 14.3	21.7 ± 13.2	112.8 ± 56.5	82.6 ± 34.8
Median	0.0	8.1	1.3	28.9	19.9	105.1	85.3
Interquartile range							
Range	(						
6 weeks							
Pts evaluated	9	14	15	15	13	14	14
Mean ± SD	0.0 ± 0.0	3.1 ± 2.0	0.4 ± 0.7	12.6 ± 9.1	8.9 ± 7.2	54.2 ± 31.2	31.0 ± 21.3
Median	0.0	2.8	0.0	12.4	7.7	49.7	29.5
Interquartile range							
Range							
Post-infustion 3[a]							
Pts evaluated	8	14	14	15	13	14	14
Mean ± SD	0.0 ± 0.0	26.4 ± 9.0	19.5 ± 9.0	90.4 ± 25.7	74.1 ± 22.1	402.1 ± 100.9	341.9 ± 92.5
Median	0.0	27.8	19.7	85.6	75.1	360.5	350.0
Interquartile range							
Range							
8 weeks							
Pts evaluated	9	13	14	15	13	14	14
Mean ± SD	0.0 ± 0.0	5.9 ± 4.7	0.7 ± 1.5	25.5 ± 12.5	19.7 ± 14.4	106.2 ± 43.7	71.5 ± 48.2
Median	0.0	5.1	0.0	24.2	13.6	110.0	68.3
Interquartile range							
Range							

[a] Samples for measuring serum infliximab concentration were collected approximately 1 hour after the end of the infusion.

concluded

Table 29 Summary of HACA response

	1 mg/kg cA2		3 mg/kg cA2		10 mg/kg cA2		All cA2-Treated Patients (n = 87)
	MTX + (n = 14)	MTX - (n = 15)	MTX + (n = 15)	MTX - (n = 14)	MTX + (n = 14)	MTX - (n = 15)	
Pts who could be evaluated	13	14	9	12	2	10	60
Pts with positive HACA response	2 (15.4%)	8 (57.1%)	1 (11.1%)	3 (25.0%)	0 (0.0%)	1 (10.0%)	15 (25.0%)
HACA titers							
1:10	0	0	1	0	0	0	1
1:20	0	0	0	1	0	1	2
1:40	0	2	0	0	0	0	2
1:80	1	2	0	1	0	0	4
1:160	1	3	0	1	0	0	5
1:2560	0	1	0	0	0	0	1
Pts with negative HACA response	11 (84.6%)	6 (42.9%)	8 (88.9%)	9 (75.0%)	2 (100.0%)	9 (90.0%)	45 (75.0%)
Pts who could not be evaluated	1	1	6	2	12	5	27
Reason:							
No post-infusion samples	0	1	0	0	0	0	1
Serum cA2 interference	1	0	6	2	12	5	26

4. Protocol C0168T15/T17: Single-Dose (T15)/ Repeat-dose treatment extension (T17) Study of Chimeric Anti-TNF Monoclonal Antibody (infliximab) in Patients with Active Rheumatoid Arthritis Who Are Receiving Methotrexate Therapy.

Methods

This was a 4-arm, multicenter, double blind, randomized, placebo-controlled, Phase 2 trial using the —— formulation (lot ——) of infliximab in subjects receiving a stable course of methotrexate 10 mg/week. In T15, a single dose of placebo, 5, 10 or 20 mg/kg iv was given and the subject monitored for 12 weeks (n= 7/dose level). In T17, 23 subjects from T15 who did have an AE received 10 mg/kg iv x 3 every 8 weeks. DMARD therapy other than MTX was not permitted. Concurrent and stable use of oral steroids or NSAIDs was permitted. Study dates: 3/95 - 11/96.

PK sampling was performed at baseline, at 1, 2 and 4 hours following the first infusion, and at day 3 and weeks 1, 2, 4, 6, 8, 10, 12 for the single-dose, blinded study. For the repeated treatment open-label extension, samples were collected at weeks 16, 20 (pre-infusion), 28 (pre-infusion), 32, 36 and 40. At week 28, samples were also drawn at the end of infusion. PK parameters were to be derived for T15 data only. HACA levels were checked before the first infusion and at weeks 4, 8 and 12 for the single-dose, blinded study and at weeks 16, 20, 28, 36 and 40 for the repeated treatment open-label extension.

Results

PK

A table of the PK parameters and the log serum concentration v. time curve after a single dose of infliximab are located on pages 20 and 21, respectively. Median Cmax rises in a dose-proportional manner from the 5 to 20 mg/kg doses. The rise in median AUC is slightly less than dose-proportional from 5 to 10 mg/kg however and dose-proportional from 10 to 20 mg/kg. Median clearance is slightly higher, and the corresponding median elimination t1/2 is slightly lower, for the 10 mg/kg dose level. The reason for this nonlinearity is not apparent. The Vd is essentially the same regardless of dose level. The concentration v. time data after repeated dosing does not add any useful information. The sponsor performed a subset analysis looking for differences in Cl or Vd based on gender, age or weight. A statistically significant (p= 0.03) weight v. median Cl effect was found where subjects in the heaviest tertile, >85 kg, had an almost 2-fold higher median Cl (13 mL/hr v. 7.3 and 7.5 mL/hr for the lowest and middle tertiles, respectively). No other significant differences were found. Upon further examination of this database (by me) as shown on page 22, this weight v. Cl effect had the greatest impact with the 5 mg/kg dose level based on median AUC. However, all of these findings are based on small sample sizes.

HACA

HACA results were not significant. Only 8/15 subjects who received infliximab during T15 had evaluable assay results and only 2 of these 8 subjects had a positive response (both with a titer of only 1:10). In T17, 9/23 subjects had an evaluable HACA result. 6/9 were HACA+ from T15 but only 2 or these 6 remained HACA+ during after T17 dose administration (all titers 1:40 or less).

C0168T15: Summary Statistics for the Derived PK Parameters

	Dose of cA2		
	5 mg/kg (n = 7)	10 mg/kg (n = 7)	20 mg/kg (n = 7)
C_{max} (μg/mL)			
Pts evaluated	7	7	7
Mean ± SD	192.1 ± 51.1	426.7 ± 106.4	907.4 ± 183.4
Median	209.0	391.0	930.0
Interquartile range			
Range			
AUC (μg/mL x hr)			
Pts evaluated	7	7	7
Mean ± SD	49909 ± 18866	78178 ± 34735	173043 ± 60691
Median	54542	82181	164732
Interquartile range			
Range			
AUC/dose (kg x hr/mL)			
Pts evaluated	7	7	7
Mean ± SD	10.0 ± 3.8	7.8 ± 3.5	8.7 ± 3.0
Median	10.9	8.2	8.2
Interquartile range			
Range			
Clearance (ml/hr)			
Pts evaluated	7	7	7
Mean ± SD	11.0 ± 7.4	11.4 ± 5.0	11.0 ± 8.9
Median	8.0	12.9	7.7
Interquartile range			
Range			
Volume of distribution at steady rate (mL)			
Pts evaluated	7	7	7
Mean ± SD	4265 ± 2529	3126 ± 716	3147 ± 635
Median	3357	3238	3136
Interquartile range			
Range			
Mean residence time (hrs)			
Pts evaluated	7	7	7
Mean ± SD	417 ± 126	313 ± 113	395 ± 194
Median	378	334	366
Interquartile range			
Range			
Terminal half life (hrs)			
Pts evaluated	7	7	7
Mean ± SD	278 ± 110	215 ± 99	295 ± 128
Median	271	191	296
Interquartile range			
Range			

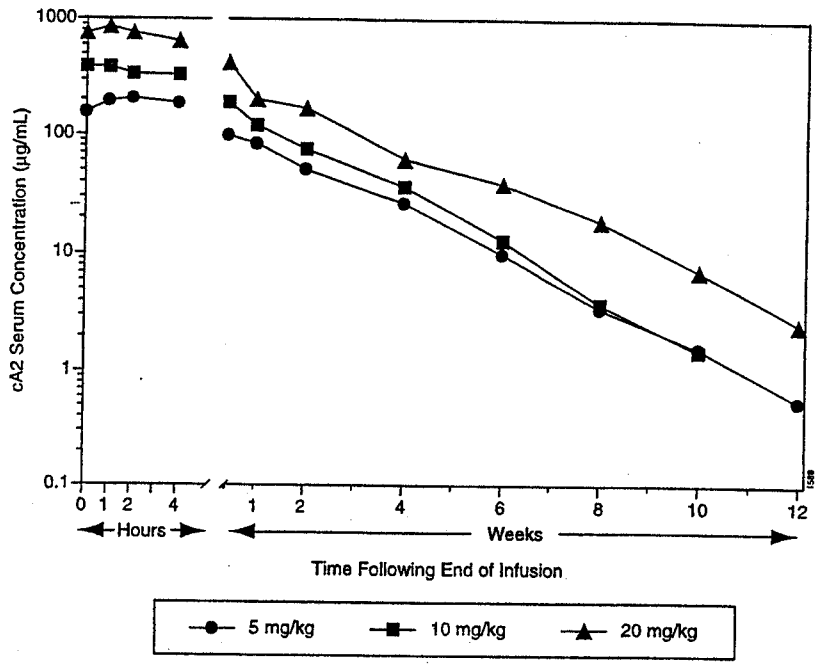


Figure 1 **Serum cA2 concentration following a single infusion of 5, 10 or 20 mg/kg cA2.** The first set of results shown after the break in the x-axis was obtained at 72 hours following the end of infusion.

21

Individual and Select Summary PK Parameters for a single dose classified by dose level and weight tertiles

dose level	subject	gender	age	wt (kg)	AUC (ug/mL*hr)	Cl (mL/hr)	Vd (mL)	MRT (hrs)	t1/2beta (hrs)	[HACA]	MEAN AUC	MEDIAN AUC	MEAN Cl	MEDIAN Cl
5 mg/kg	3008										56624	56624	5.8	5.8
	1001													
	2001										60842	57918	6.4	6.1
	2010													
	3012													
	2007										36737	38147	17.2	17.0
	3004													
10 mg/kg	1002													
	2011										66334	70093	11.8	11.2
	3005													
	3010													
	2002													
	2005										93971	82181	10.9	12.9
	3001													
20 mg/kg	2008										163972	163972	7.1	7.1
	3002													
	1003													
	2004										201050	188327	8.0	8.1
	2013													
	3006													
	3009										79158	79158	31.0	31.0

KEY: lowest tertile: <70 kg middle tertile: 70-85 kg highest tertile: >85 kg

22

5. Protocol C0168T18: Tumor Necrosis Factor (TNF) Blockade in Patients with Rheumatoid Arthritis: Mechanisms of Action.

Methods

This was an open-label, single center study in 10 subjects with active rheumatoid arthritis given a single dose of 10 mg/kg iv. The pertinent goal was to compare the PK profile of 2 formulations, — and lyophilized. 5/10 subjects received the to-be-marketed lyophilized formulation while the remaining 5 received the — formulation.

Subjects were not required to stop DMARDs provided a stable therapy was maintained during the study. Stable oral steroids or NSAIDs use was permitted. Serum samples for PK were collected at predose, and at 1 hour, 1, 2, 4 and 12 weeks postdose. PK parameters were derived. HACA levels were checked at baseline and at week 12.

Results

Individual serum infliximab data and a summary of derived PK parameters were submitted. As shown below, exposure was greater with the — formulation based on median Cmax (221 v. 168 ug/mL) and median AUC (52426 v. 49056 ug/mL*hr). The difference in the AUC was not statistically significant (p= 0.903) according to the sponsor and is not clinically significant either. The lyophilized formulation has a longer median elimination half life (278 hr v. 186 hr), most likely due to the smaller Cl given that the Vd is similar for the 2 formulations. However, these results are of limited value because they are based on sample sizes that are small, the use of only a single dose, and the inconsistent concomitant use of MTX between subjects. The difference in the elimination t1/2 may eventually translate into an increased chance of maintaining therapeutic levels for a longer period of time during the q 8 week dosing regimen. The very small size of the database also precludes a look for Cl v. gender or exposure v. gender effects. 6/10 subjects were evaluable for a HACA response; none had a positive response. There are no obvious PK and/or clinically significant differences between the — and lyophilized formulations that could affect the approval or labeling of infliximab based on the data submitted.

T18: Summary statistics of the PK parameters calculated using the raw subject data submitted in the BLA

FORMULATION 10 mg/kg

subject	Cmax (ug/mL)	AUC (ug/mL*hr)	Cl (mL/hr)	Vd (mL)	MRT (hrs)	t1/2beta (hrs)
1001						
1002						
1003						
1005						
1007						
mean	224	45353	22	5415	245	189
median	221	52426#	18.5	3909	212	186
SD	66	13181	11	3221	65	22

LYOPHILIZED FORMULATION 10 mg/kg

Subject*	Cmax (ug/mL)	AUC (ug/mL*hr)	Cl (mL/hr)	Vd (mL)	MRT (hrs)	t1/2beta (hrs)
1004						
1006						
1009						
1010						
mean	175	46691	15	5899	394	286
median	168	49056#	15.45	5729.5	408.5	278
SD	24	12102	3	937	60	105

* no data available for 1008

\# AUCliq v. AUClyo was not statistically significant (p= 0.903) according to the sponsor

6. **Protocol C0168T22: A placebo-controlled, double-blinded, randomized clinical trial of anti-TNF chimeric monoclonal antibody (cA2; infliximab) in patients with active rheumatoid arthritis despite methotrexate treatment (ATTRACT).**

Methods

This is a 5-arm, multicenter, Phase 3 study in subjects with rheumatoid arthritis who are on a stable dose of at least 12.5 mg/week of methotrexate. The dose levels are placebo, 3 or 10 mg/kg iv. All dose levels are given at week 0, 2 and 6 followed either by every 4 week dosing thereafter (placebo, 3 and 10 mg/kg) or every 8 weeks thereafter (3 or 10 mg/kg). The lyophilized formulation is being administered (lots [redacted] and [redacted] DMARD therapy other than MTX was not permitted. Concurrent and stable use of oral steroids or NSAIDs was permitted. Study dates: 3/97 - ongoing; the results from 3/97 to 8/98 (n= 200) have been submitted in this BLA.

Blood sampling for the measurement of serum infliximab concentration is performed at: trough for each infusion through week 6 and then every 8 weeks through week 30. Peak samples are collected 1 hour postdose during weeks 0, 2, 6, and 14. There are no plans to derive PK parameters; only summary statistics for the concentration v. time data are to be presented. In coordination with 2 blood samplings, a 24 hour urine collection was performed after the first dose in a subset of subjects (blinded selection) to look at urinary excretion. A HACA level was checked at baseline but there was no indication of further HACA level monitoring unless the subject prematurely withdrew from the study.

Results

This sBLA contains the data through week 30 for the first 200 patients enrolled in the study. Any subject who did not receive all infusions or received the wrong dose was not included in the analyses from that point onward. The concentration v. time summary statistics and corresponding graphs located on pages 26-29 indicate dose-linearity of the 3 and 10 mg/kg iv dose level for both the every-4-week and the every-8-week regimens. Steady state appears to be achieved by week 14 for the proposed dosing regimen of every-8-weeks. Steady state median trough is 0.8 ug/mL for the 3 mg/kg iv q 8 week dosing regimen. HACA results are not available.

Since the subjects for the urine collection were blindly selected, only 11/17 were actually on infliximab (n= 9 for the 3 mg/kg group, and n= 2 for the 10 mg/kg group). As expected, no infliximab was found in the urine during the 24 hours after the first dose.

The graphs on page 29 compare the various classifications of efficacy response to the infliximab log serum concentration v. time curves for each studied dosing regimen. There is no apparent dose-response or concentration-response for any of the 4 dosing regimens.

BLA 99-0128

Table 16 Serum concentration of infliximab through week 6[a]

	Dose of Infliximab					
	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	3 mg/kg combined	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks	10 mg/kg combined
Pts randomized	40	41	81	39	40	79
Week 0 (1 hr post-infusion)						
Pts evaluated	40	40	80	37	39	76
Mean ± SD	65.2 ± 16.0	67.4 ± 14.1	66.3 ± 15.0	224.4 ± 83.0	237.7 ± 103.9	231.2 ± 93.9
Median	64.8	65.7	65.1	219.3	212.5	215.4
Interquartile range						
Range						
Week 2 (pre-infusion)						
Pts evaluated	40	40	80	39	36	75
Mean ± SD	14.2 ± 5.4	15.8 ± 9.1	15.0 ± 7.5	52.4 ± 18.0	45.7 ± 17.9	49.2 ± 18.2
Median	14.6	14.5	14.5	48.7	45.2	47.0
Interquartile range						
Range						
Week 2 (1 hr post-infusion)						
Pts evaluated	40	39	79	38	39	77
Mean ± SD	79.9 ± 23.1	82.0 ± 18.1	80.9 ± 20.7	313.8 ± 144.4	291.7 ± 130.1	302.6 ± 136.9
Median	76.1	81.5	78.4	284.5	264.6	271.7
Interquartile range						
Range						
Week 6 (pre-infusion)						
Pts evaluated	39	39	78	39	40	79
Mean ± SD	8.4 ± 6.2	8.4 ± 5.9	8.4 ± 6.0	38.2 ± 18.3	30.9 ± 18.5	34.5 ± 18.6
Median	8.8	7.6	7.8	37.1	28.4	33.9
Interquartile range						
Range						
Week 6 (1 hr post-infusion)						
Pts evaluated	38	39	77	39	40	79
Mean ± SD	76.0 ± 30.0	77.0 ± 20.4	76.5 ± 25.4	300.7 ± 143.8	280.8 ± 116.6	290.6 ± 130.3
Median	67.7	74.7	72.7	268.2	245.8	254.3
Interquartile range						
Range						

[a] Infliximab is measured in µg/mL.

Table 17 Serum concentration of infliximab from week 14 through week 30[a]

	Dose of Infliximab			
	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks
Pts randomized	40	41	39	40
Week 14 (pre-infusion)				
Pts evaluated	35	36	38	39
Mean ± SD	3.1 ± 7.6	6.5 ± 6.2	10.8 ± 8.8	28.6 ± 21.2
Median	1.2	4.9	8.9	22.9
Interquartile range				
Range				
Week 14 (1 hr post-infusion)				
Pts evaluated	34	36	39	39
Mean ± SD	64.0 ± 20.5	72.2 ± 14.1	260.1 ± 121.6	276.7 ± 105.9
Median	60.9	71.5	230.2	239.9
Interquartile range				
Range				
Week 22 (pre-infusion)				
Pts evaluated	32	33	37	35
Mean ± SD	1.2 ± 1.4	9.9 ± 8.7	11.2 ± 11.9	37.4 ± 25.5
Median	0.8	8.2	8.4	34.2
Interquartile range				
Range				
Week 30 (pre-infusion)				
Pts evaluated	29	32	34	35
Mean ± SD	1.5 ± 1.6	9.7 ± 8.6	8.9 ± 8.1	35.8 ± 23.7
Median	0.5	7.8	6.9	33.1
Interquartile range				
Range				

[a] Infliximab is measured in µg/mL.

The median infliximab serum concentrations are graphically displayed in Figure 2. Reproducible patterns of serum infliximab concentrations were observed for all treatment groups. Median peak infliximab concentrations ranging from 60.9 to 81.5 µg/mL were

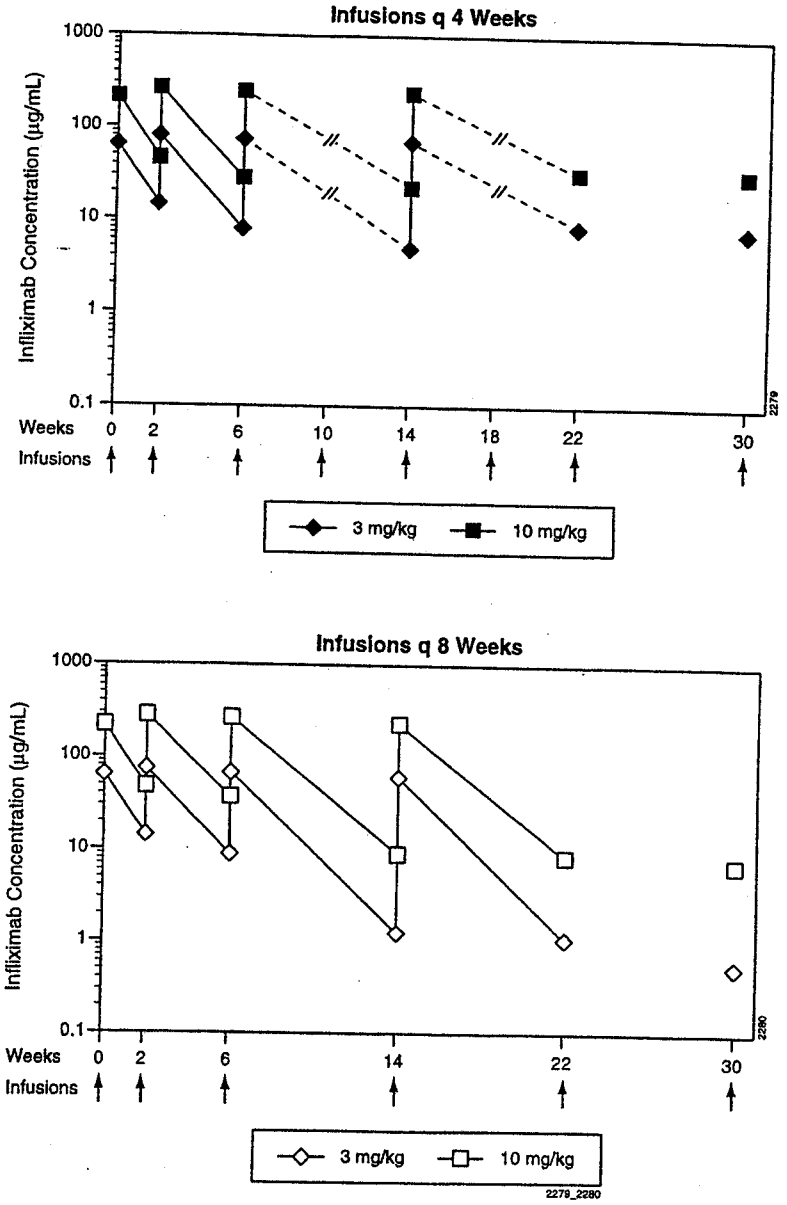


Figure 2 **Median serum infliximab concentrations over time.** The median infliximab serum concentrations over time for the 3 mg/kg (closed diamond) and 10 mg/kg (closed squares) treatment groups administered q 4 wks following week 6 are shown in the top panel. The median serum concentrations for the 3 mg/kg (open diamond) and 10 mg/kg (open squares) treatment groups administered q 8 wks following week 6 are shown in the bottom panel. The dashed lines and hash marks are shown in the top panel to indicate that there was an infusion at weeks 10 and 18 for which no serum samples were collected. There is no line connecting the treatments at week 22 and week 30 because no post-infusion samples were collected at week 22.

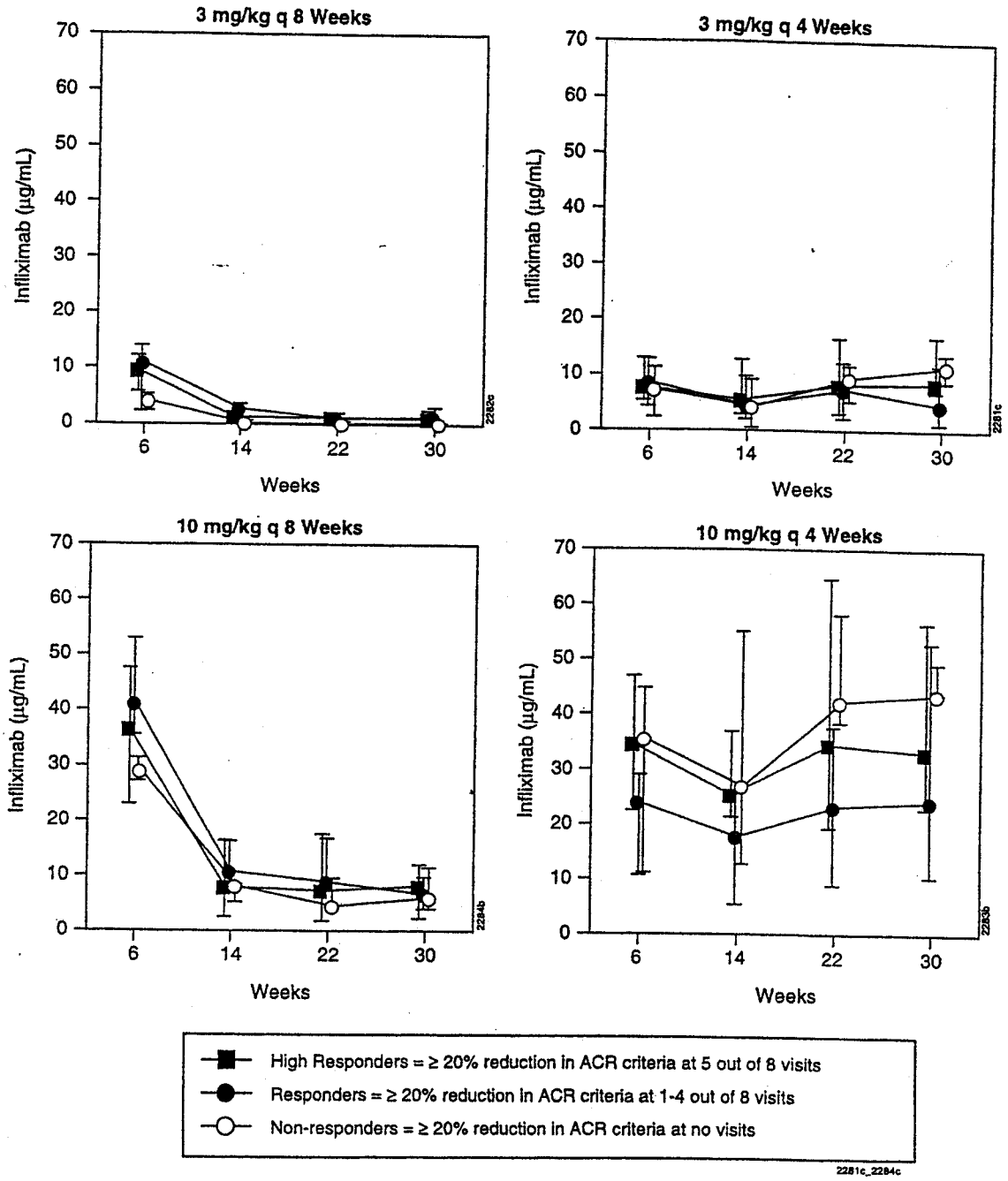


Figure 17 **Median serum concentrations for samples collected 4-8 weeks following treatment in responders and non-responders in C0168T22.** The median and interquartile range serum concentrations for high, moderate and non-responding patients in C0168T22 are shown. High responders achieved ≥20% ACR response in ≥ 5 out of 8 response evaluation visits. Moderate responders achieved ≥20% ACR response in ≥ 1 and ≤ 4 out of 8 response evaluation visits while non-responders achieved ≥20% ACR response in 0 out of 8 response evaluation visits.

Additional Issues:

1. Greater elevation of ALT/AST seen with infliximab plus MTX compared to with MTX only.

   During her clinical review of the safety database for Protocol T22, Dr. Barbara Matthews noted that subjects who received infliximab plus MTX appeared to have slightly higher elevations in ALT/AST than subjects who received MTX alone. The sponsor performed a subset analysis of these LFT elevations based on MTX dose but the sample size per dose group was too small to be very helpful. Dr. Matthews also noted a slightly higher incidence of ulcerative stomatitis in the infliximab plus MTX group compared to the MTX only group (ulcerative stomatitis is a well-known AE for MTX). The safety database from T14 showed higher elevations of ALT/AST in the 1 and 3 mg/kg infliximab plus MTX groups compared to the infliximab alone group. Dr. Matthews also looked at the safety database for the subjects with Crohn's disease. Most of these subjects did not receive concurrent MTX, and elevations in the ALT/AST were not seen.

   The above findings suggest the possibility of an infliximab-related change in the PK of MTX leading to an increase in MTX-related AE's. Unfortunately, serum MTX levels were not monitored in the submitted protocols (and are not routinely monitored in clinical practice). A mechanism for a possible change in MTX PK is not apparent. Presently, this finding, and the lack of data to explain it, does not affect the approval of infliximab for this new indication. It is prudent, however, to include a statement in the labeling to increase awareness and potentially enhance vigilance in the medical community--- particularly since the proposed indication specifically calls for the concurrent use of MTX. A drug-drug interaction study may be warranted in the future if the results of post-marketing surveillance indicate a stronger trend.

2. Potential for AE's (serum sickness) with retreatment.

   This concern was also raised by Dr. Barbara Matthews and pertains more to potential safety issues upon re-initiation of infliximab administration, particularly with regards to the formation and/or presence of HACA. The sponsor addressed this issue in the Clinical Pharmacology section of the sBLA. The subset analysis was performed on subjects from only protocols T09 and T15/17 because the majority of subjects in protocol T14 had a detectable infliximab level during retreatment and hence the HACA titer could not be determined. There are no results presently from protocol T22 because the study (and hence dose administration) is ongoing. The resultant database of evaluable subjects from T09 and T15/17 can be found in Appendix 1. There does not appear to be a relationship between infusion reaction and dose or HACA titer, however, the database is too small (n= 15) to drawn any conclusions with confidence. This database is also limited because the majority (14/15) of subjects did not receive concomitant MTX, and thus the database is not representative of the population in the proposed indication. For similar reasons, it is impossible to ascertain the role of the formulation (v. lyophilized), or the presence/absence of MTX in the incidence of re-initiation AE's.

Summary:

1. Protocols T14 and T22 provide the most useful PK data for the sBLA. The data generally support a dose-proportional PK profile for the 3 and 10 mg/kg dose levels of infliximab plus MTX.

2. There is no apparent dose-efficacy response or concentration-efficacy response for either the 3 or 10 mg/kg dose level when given every-4-weeks or every-8-weeks. A dramatic decrease in serum infliximab concentration for the 1 mg/kg dose given without concurrent MTX use was associated with a sharp decrease in efficacy. HACA formation is the most likely reason for the increase in elimination of infliximab. The PK data for the to-be-marketed 3 mg/kg dose level did not demonstrate the same degree of decline in the absence of concurrent MTX use.

3. Infliximab exposure based on AUC is consistently lower when infliximab is administered without concomitant MTX compared to combination treatment (T14). This difference in exposure between infliximab only and combination treatment was dose-dependent with the largest difference seen at the 1 mg/kg dose level.

4. HACA formation is associated with an increase in infliximab clearance and a decrease in exposure based on AUC when MTX is not co-administrated (T09). This increase in clearance is dose-dependent with the highest clearance seen with the 1 mg/kg dose level. Concurrent use of MTX appears to dampen this HACA formation and the resultant decrease in exposure but its affect on the clearance can not be quantitated with the PK data submitted in this sBLA (T14).

5. A difference in clearance or volume of distribution based on age or weight was not seen. Insufficient data were submitted to determine if baseline renal or hepatic function has an affect on the clearance or volume of distribution. A statistically significant difference in clearance was seen by gender across a single dose range of 1 - 10 mg/kg. Regardless of HACA status, males have a higher median clearance than females after a single dose of 1, 3 or 10 mg/kg of infliximab without concurrent MTX use (T09).

6. Insufficient data are available to comment upon the trend noted in the safety database of a greater frequency of liver function enzyme elevation and stomatitis (known MTX-related AE's) in subjects receiving infliximab and MTX compared to those subjects receiving infliximab alone. If warranted based on post-marketing surveillance, a formal drug-drug interaction study could be conducted.

7. The potential for AE's (serum sickness) upon re-initiation of infliximab therapy is unknown due to the lack of a database comprised of the pertinent population that is of sufficient size.

Conclusions:

The PK results submitted in this sBLA do not present a barrier to licensure of the proposed dosing regimen of the 3 mg/kg dose of infliximab. The Pediatric Rule applies to this sBLA and been addressed with the sponsor by Dr. Barbara Matthews.

Lori A. Paserchia, MD
Clinical Pharmacology Reviewer

11/1/99

Table 19 Effect of repeated administration of infliximab in HACA-positive patients

Patients with NO Infusion Reactions

Patient #	Dose(mg/kg) Inf #1	Peak Titer Post Inf #1	Peak Efficacy[a] Post Inf #1	Dose(mg/kg) Inf #2	Full Dose Received?	Peak Titer Post Inf #2	Peak Efficacy Post Inf #2
02018							
03010							
03012							
02001							
03001							
04011							

Patients with Infusion Reactions

Patient #	Dose(mg/kg) Inf #1	Peak Titer Post Inf #1	Peak Efficacy Post Inf #1	Dose(mg/kg) Inf #2	Full Dose Received?	Peak Titer Post Inf #2	Peak Efficacy Post Inf #2
01019							
02015							
04019							
01015							
02014							
02017							
02010*							
03009*							

Patients with SERIOUS Infusion Reactions

Patient #	Dose(mg/kg) Inf #1	Peak Titer Post Inf #1	Peak Efficacy Post Inf #1	Dose(mg/kg) Inf #2	Full Dose Received?	Peak Titer Post Inf #2	Peak Efficacy Post Inf #2
01004							

* Patients enrolled in C0168T15/17

[a] Peak efficacy defined as the highest score meeting or exceeding 20% Paulus or 20% ACR criteria following an infusion in C0168T09 or C0168T15/17, respectively.

[b] Not determined.

[c] Patient also received two subsequent 10 mg/kg infusions in C0168T17

[d] Efficacy value observed following infusion #4

[e] Patient only received 9.9 mg, no further treatments administered